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Self Micro-emulsifying Drug Delivery System: A Promising Technique to Enhance the Solubility of Lipophilic Drugs

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ABSTRACT

Oral route of administration has been favoured route and has dominated over other routes of administrations. However this chosen route is restricted to those drugs molecule that are permeable across the gastric mucosa and are at least sparingly soluble. Approximately 40% of new chemical molecules exhibit poor aqueous solubility and exhibit a foremost challenge to modern drug delivery system, because of their low bioavailability due to its solubility. The solubility of poorly water-soluble drugs can be enhanced by incorporating active pharmaceutical ingredients into oral lipid-based drug delivery systems. Self-micro emulsifying oil formulations are mixture of synthetic or natural oil, liquid or solid surfactant, hydrophilic solvent and co-surfactant. It offers advantages like simplicity to manufacture, convenience in scale-up, less interference of food on the dosage form and has the capability to deliver peptides. ying drug delivery systems (SMEDDS). SMEDDS have gained exposure for their ability to increase solubility and bioavailability of poorly soluble drugs. SMEDDS, which are isotropic mixtures used for the design of formulations to improve the oral absorption of highly lipophilic drug compounds. Conventional SMEDDS are mostly prepared in a liquid form, which can have some disadvantages. SMEDDS can be orally administered in soft or hard gelatin capsules and form fine relatively stable oil-in-water emulsions. Solid-SMEDDS are prepared by solidification of liquid/semisolid self-micron emulsifying ingredients into powders, have gained popularity. This article gives a complete overview of SMEDDS, but special attention has been paid to formulation, design, evaluation, and little emphasis on application of SMEDDS.

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INTRODUCTION

The oral route is the uncomplicated and most favorable way of non-invasive administration. Oral drug delivery systems being the most cost-effective have always led the worldwide drug delivery market. This oral route might cause an obstacle for drug molecules exhibiting poor aqueous solubility. When a drug is administered by the oral route the first step for it to get absorbed is its solubilization followed by permeation.[1] The poor water solubility and the oral delivery of such drugs are frequently associated with implications of lack of dose proportionality, low bioavailability, and high intra- and inter-subject variability.[2]

Favored formulation approaches used for delivering drugs with poor aqueous solubility include:

- Micronization of crystalline solids
- Amorphous formulation or solid dispersions and
- Lipid-based formulations.

Only lipophobic drugs are solubilized easily, highly lipophilic drugs are difficult to solubilize, and they can be dissolved by using various oils. There are several solubility enhancement techniques such as co-solvency, salt formation, solid dispersion, SMEDDS, SNEDDS, emulsion, etc.[3] Among these approaches, lipid-microemulsion formulations, with a particular emphasis on self-emulsifying drug delivery systems (SEDDS or SMEDDS), have gained great importance as a promising approach for poorly soluble drugs as well as for natural compounds.[4] SMEDDS is a class of emulsion that has received precise attention as a mode for enhancing the oral bioavailability of drugs. These systems consist of oil, surfactant & co-

surfactant that form emulsions on mixing with water with little or no energy input.[5] SMEDDS or self-emulsifying oil formulations (SEOF) are termed isotropic mixtures of natural or synthetic oils, solid or liquid surfactants, one or more hydrophilic solvents, and co-solvents/surfactants. Upon mild agitation followed by dilution in aqueous media, such as GI fluids, these systems develop into fine oil-in-water (o/w) emulsions or microemulsions.[6] Self-emulsifying formulations spread rapidly in the GI tract, and the peristalsis action of the stomach and the intestine provides the agitation necessary for self-emulsification. SMEDDS form transparent microemulsions with a droplet size ranging between 100-250 nm. SMEDDS are thermodynamically stable formulations that are easy to produce. Hence, for hydrophobic drug compounds that display dissolution rate-limited absorption, these systems may offer an enhancement in the rate and extent of absorption and result in more reproducible blood-time profiles.[7] Dispersion of oil in water, of most interest for pharmaceutical applications, is referred to as an oil-in-water (o/w) emulsion, which requires the emulsifying agent to be typically more soluble in the aqueous phase. The reverse emulsion, water-in-oil (w/o) are stabilized with the help of surfactants that are stable in the oil phase.[8]

HISTORY OF MICRON EMULSIONS:

The term microemulsion was first coined by T. P. Hoar and J. H. Shulman in the year 1943 professors of chemistry at Cambridge University. Other names for these systems are often termed as transparent emulsion, swollen micelle, micellar solution, and solubilized oil. Microemulsions are formed when:

1. The interfacial tension at the oil/water interface is brought to a very low level.
2. The interfacial layer is kept highly flexible and fluid. [9]

These two conditions are usually met by a careful and detailed choice of the components and of their respective proportions and by the use of a "co-surfactant" which brings elasticity to the oil/water interface. These circumstances lead to a thermodynamically enhanced structure that is stable as it differs from the conventional emulsions and does not require high input of energy (i.e. through agitation) to be formed. Because the size of the particles is minute which makes microemulsions transparent and their structure cannot be observed through the naked eye.[10]

NEED OF SMEDDS:

In the Oral delivery of poorly aqueous-soluble drugs, first is to pre-disperse the drug in a suitable solvent and fill the formulation into capsules. The prime advantage of this method is that pre-dispersing the drug helps overcome the initial rate-limiting step of particulate dissolution in the aqueous environment within the GI lumen. If the drug is dissolved in a lipid vehicle, there are fewer chances for precipitation on dilution in the GI lumen, as partition kinetics will aid the drug residual in the lipid droplets. Another tactic for poorly soluble drugs is to formulate in a solid solution using an aqueous soluble polymer to assist the solubility of the drug compound. [11]

ADVANTAGES OF SMEDDS:

Improvement in oral bioavailability:

Dissolution rate dependant absorption is a major factor that limits the bioavailability of plentiful poorly aqueous soluble drugs. The ability of SMEDDS to exhibit the drug in GI lumen in solubilised and micro emulsified form and consequent rise in specific surface area aids more efficient drug transport through the intestinal aqueous boundary layer and through the absorptive brush border membrane leading to improved bioavailability.[12]

Reduction in inter-subject and intra-subject variability and food effects:

There are several drugs which show large inter-subject and intra-subject variation in absorption leading to decreased performance of drug and patient non-compliance. Food is a major factor altering the therapeutic working of the API in the body. SMEDDS are a boon for such drugs.[12]

Ease of manufacture and scale-up:

Ease of manufacture and scaleup is one of the most important advantage that makes SMEDDS unique when compared to other drug delivery systems like solid dispersions, liposomes, nanoparticles, etc., dealing with improvement of bio-availability. SMEDDS require very simple and economical manufacturing facilities like simple mixer with agitator and volumetric liquid filling equipment for large-scale manufacturing. This explains the interest of industry in the SMEDDS.[12]

Ability to deliver peptides that are prone to enzymatic hydrolysis in GIT:

One unique property that makes SMEDDS superior as compared to the other drug delivery systems is their ability to deliver macromolecules like peptides, hormones, enzyme substrates and inhibitors and their ability to offer protection from enzymatic hydrolysis. The intestinal hydrolysis of prodrug by cholinesterase can be protected if polysorbate 20 is emulsifier in micro emulsion formulation. [13] These systems are formed spontaneously without aid of energy or heating thus suitable for thermolabile drugs such as peptides. [13]

No influence of lipid digestion process:
Unlike the other lipid-based drug delivery systems, the performance of SMEDDS is not influenced by the lipolysis, emulsification by the bile salts, action of pancreatic lipases and mixed micelle formation. SMEDDS are not necessarily digested before the drug is absorbed as they present the drug in micro-emulsified form which can easily penetrate the mucin and water unstirred layer.[14]

Increased drug loading capacity:
SMEDDS also provide the advantage of increased drug loading capacity when compared with conventional lipid solution as the solubility of poorly water soluble drugs with intermediate partition coefficient (2<logP>4) are typically low in natural lipids and much greater in amphilic surfactants, co surfactants and co-solvents.[15S]

ADVANTAGES OF SMEDDS OVER OTHER EMULSIONS:

1. Storage:
SMEDDS has the same advantage as emulsions, of facilitating the solubility of hydrophobic drugs. Macroemulsions undergo creaming over a period of time, whereas SMEDDS being thermodynamically stable can be stored easily.[15] The major difference between the above microemulsions and common emulsions lies in the particle size of droplets. The size of the droplets of common emulsion ranges between 0.2 and 10 µm, and that of the droplets of microemulsion formed by the SMEDDS generally ranges between 2 and 100 nm (such droplets are called droplets of nano particles). Since the particle size is small, the total surface area for absorption and dispersion is significantly larger than that of solid dosage form and it can easily penetrate the gastrointestinal tract and be absorbed. The bioavailability of the drug is therefore improved.[16]

2. Stability:
In contrast to micro/nanoemulsions, SMEDDS do not contain water and hence, they have improved physical and/or chemical stability on long-term storage. Self-nanoemulsifying tablets of carvedilol showed successful incorporation of carvedilol within the SNEDDS. This resulted in improvement of the stability of carvedilol on dilution with aqueous media in the presence of cellulosic polymers.[17]

3. SMEDDS offer numerous delivery options like filled hard gelatin capsules or soft gelatin capsules or can be formulated in to tablets whereas emulsions can only be given as an oral solutions.
4. Emulsion cannot be autoclaved as they have phase inversion temperature while SMEDDS can be autoclaved.

DISADVANTAGES OF SMEDDS:
Even though SMEDDS preparation offers many benefits, despite it there are some restrictions that are affiliated with this product. Some challenges associated with SMEDDS formulations.

1. The precipitation of drug molecules at the time of dilution: The diluted SMEDDS go through the precipitation of active substances in the GI fluid. However, the developed lipid systems should have one more important characteristic such as they should maintain active drug molecules in a solubilized state in the GI tract. Moreover, the precipitation of an active substance in the system diminishes the benefit that is usually provided by the lipid-containing preparations.[18]
2. Lack of good predicative in vitro models for assessment of the formulations.
3. This in vitro model needs further development and validation before its strength can be evaluated.[19]

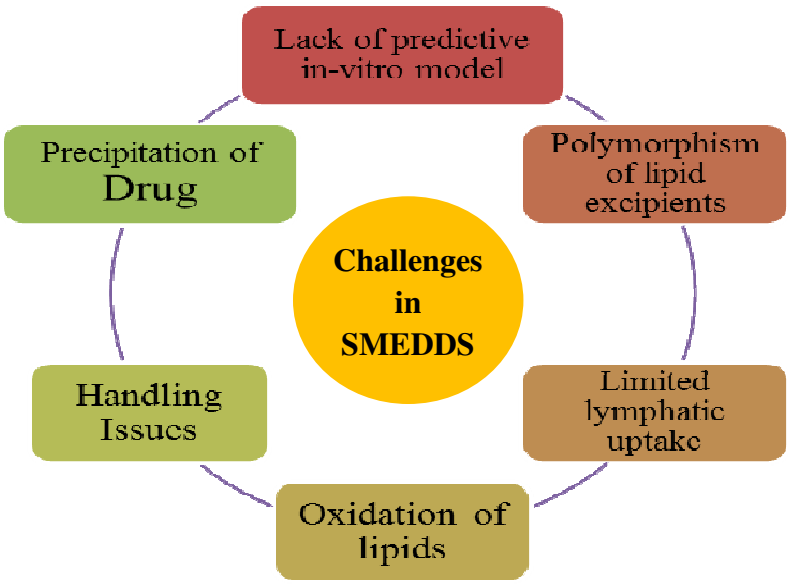


FIGURE 1. Challenges in SMEDDS formulation.

4. Moreover, volatile cosolvents in the conventional self microemulsifying formulations are known to migrate into the shells of soft or hard gelatin capsules, resulting in the precipitation of the lipophilic drugs.[20]

MECHANISM OF SMEDDS:

The emulsion is stabilized by the surfactant molecules that form a film around the internal phase droplet. In case of SMEDDS, the free energy of formation is very low and positive or even negative which results in thermodynamic spontaneous emulsification. It has been suggested that self-emulsification occurs due to penetration of water into the liquid crystalline (LC) phase that is formed at the oil/surfactant-water interface into which water can penetrate assisted by gentle agitation during self-emulsification. After water penetrates to a certain extent, there is disruption of the interface and a droplet formation. This LC phase is considered to be responsible for the high stability of the resulting microemulsion against coalesce.[21]

$$\Delta G = \Sigma N \pi r2 \sigma$$

Where,
N --- Number of droplets,
r --- Radius of droplets,
σ --- Interfacial energy,
ΔG --- free energy associated with the process.[22]

BIOPHARMACEUTICAL ASPECTS:

An extensive literature survey explains that the use of lipid increases the bioavailability by depleting gastric transit and thus increasing gastric resistance time.

1. Enhanced secretion of bile salt (BS) with endogenous biliary lipids consisting of phospholipids (PL) and cholesterol (CH) promotes the formation of BS/PL/CH intestinal mixed micelles, which enhance the solubility of GI fluid and ultimately increase the solubility of the poorly water-soluble drug. The addition of exogenous lipids in bile salts swells the micellar structure and enhances the solubilization capacity.[23]
2. In SMEDDS formulations, the drugs which are having high lipophilic nature can bypass the lymphatic transport and enhance the bioavailability directly or by decreasing first-pass metabolism.[24]
3. Changes in the biochemical barrier function of the GI tract. It is clear that certain lipids and surfactants may attenuate the activity of intestinal efflux transporters as indicated by the p-glycoprotein efflux pump and thus reduce the extent of enterocyte based metabolism.[25]
4. Alterations (reduction) in gastric transit thereby slowing delivery to the absorption site and increasing the time available for dissolution.[26]

CLASSIFICATION OF LIPIDS USED IN OLDDS (ORAL LIPID-BASED DRUG DELIVERY SYSTEM):

Lipids are classified into different types depending upon use in OLDDS appropriately for poorly water soluble and lipophilic drug.

Type I:

Type I system consists of mainly oils i.e., without surfactants. Type I lipids support drug transfer into the colloidal aqueous phase and facilitate the amphiphilic lipid digestion by pancreatic lipase/ co-lipase. In type I, triglycerides composition consists of 100%, with coarse particle size. The advantage of this system is that the excipients which are utilized in this system are generally regarded as safe, simple, and compatible for solid dosage forms such as capsules. However, the disadvantage associated with this system is poor solvent capacity unless the drug is highly lipophilic.[27]

Type II:

Type II system consists of isotropic mixtures of lipid and lipophilic surfactants which have the ability to self-emulsify and to form fine o/w emulsions when introduced in aqueous media. Surfactant concentration above 25% (w/w) causes self-emulsification which can be increased to 50- 60% (w/w). Digestion of SEDDS starts after contact with the gastrointestinal tract. To formulate convenient unit dosage forms of the drugs with poor aqueous solubility, formulated SEDDS could be encapsulated into hard or soft gelatine capsule.[28]

Type III:

Formulations consist of SMEDDS, which are further subdivided into Types IIIA and IIIB. Type IIIB consists of increased concentration of hydrophilic surfactants and co-solvents and lesser quantity of lipid in comparison to Type II. Type IIIB formulations are more susceptible toward a greater risk of drug precipitation on dispersion owing to their elevated content of surfactant and co-solvent.[29]

Type IV:
Forms a clear micellar solution on dispersion, likely loss of solvent capacity on dispersion unlikely to be digested consists of Water-soluble surfactants and co-solvent (oil free).[30]

THE COMPOSITION OF SMEDDS FORMULATION:

Drug:
SMEDDS is a choice of formulation for the drug with high lipophilicity and low dose. The solubility of the drug in the oil phase decides the performance of the SMEDDS as the drug should remain in solubilized form. Drugs with low lipid solubility and high doses are unsuitable for SMEDDS formulation. If a high dose of the drug is soluble in one of the components of the SMEDDS, particularly oil, then it can be formulated into SMEDDS.[31] Lipophilicity and dose of the drug are the main criteria to be considered before development of SMEDDS formulation. Ideally, drug should have low dose, log P>2 and should not possess extensive first pass metabolism.

Oils:
Oil is an important ingredient used in the SMEDDS formulation. The lipophilic drugs are solubilised by oils and it promotes self-emulsification and the transport of lipid soluble drug in the small intestine is promotes by oils. Only 40-80% concentration of oil is used in SMEDDS formulation.[32] In order to make SMEDDS systems pharmaceutically acceptable, it is necessary to prepare such systems by using nontoxic and safe components. Oil from natural sources and their derivatives, e.g. triglycerides and fatty acid methyl esters. An acceptable lipophilic phase for pharmaceutical uses would be vegetable oils. The extension of a microemulsion region generally depends on nature of oil. This is due to differences in oil penetration into the surfactant layer.[33]

Example: Castor oil, Sunflower oil, Olive oil, Seseam oil, Hydrogenated specialty oils.

Surfactants:
Surfactants form the interfacial film and lower the interfacial tension to a small value which facilitates dispersion process. HLB value and concentration of surfactant is essential to be considered while selecting a surfactant. For attaining high emulsifying performance, the emulsifier involved in the formulation of SMEDDS should have high HLB greater than 12 which assists in formation of small o/w droplets and rapid spreading of formulation in aqueous media. Generally, non-ionic surfactants with HLB>12 are suggested for design of self-dispersing systems as these are less toxic than ionic surfactants.[34]

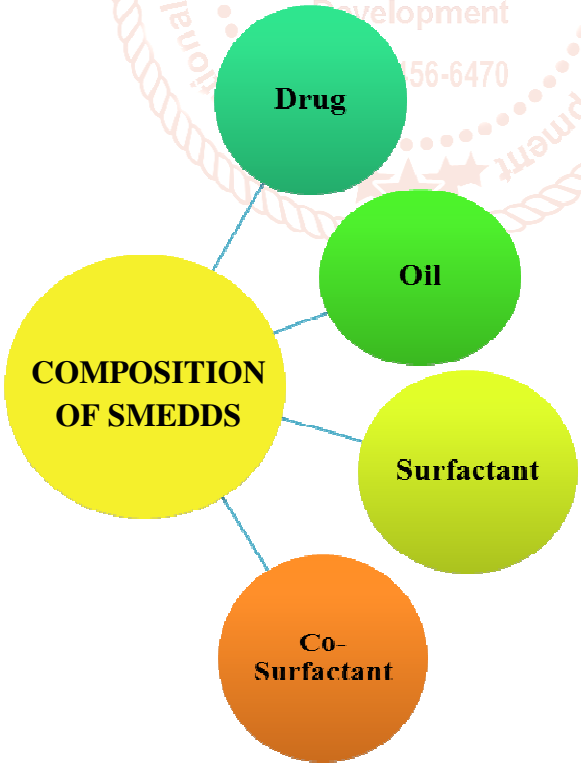


FIGURE 2: THE COMPOSITION OF SMEDDS FORMULATION

Attempts have been made to rationalize surfactant behavior in terms of the hydrophile-lipophile balance (HLB), as well as the critical packing parameter (CPP). The CPP relates the ability of surfactants to form particular aggregates to the geometry of the molecule itself. The analysis of film curvature for surfactant association leading to microemulsion formation has been explained by Isaraelachvili.

In terms of the packing ratio, P

$$P = Vo/AoLo$$

Where,
Vo = partial molar volume of the surfactant.
Ao= cross sectional area of the surfactant head group.
Lo = maximum length of the surfactant chain.[35]

Example:
Cremophor RH 40, Labrafil M 1944 CS, Acryosol K-150, Labrasol ,Tween 60, Span 60, etc.

Co-surfactant:
Surfactants are used to reduce the interfacial tension or surface tension, In SMEDDS high concentration surfactants are used which produce harmful effect, in order to reduce that effect co-surfactants are used. The selection of surfactant and co-surfactant is based on the drug which is used for SMEDDS formulation and solubility of the drug molecules. HLB vale of co-surfactant should be 10-14. The large amount of drug or hydrophilic surfactant can be dissolved by organic solvents such as poly-ethylene glycol, ethanol and propylene glycol, so they can be uses as a co-surfactant in SMEDDS formulation. Some volatile co-solvent and alcohols may penetrate into the outer shells of hard /soft gelatin capsule result in degradation of drug. Hence proper selection of co-surfactant should produce good SMEDDS formulation. [36]

FORMULATION OF SMEDDS:

FIGURE 3: FORMULATION OF SMEDDS

1. **Screening of Excipients**:

➢ **Solubility Study**:

The solubility of drugs is determined in different oils, co-surfactants, and surfactants. An excess quantity of the drug is added in 2 ml of each of the selected oil, co-surfactants, and surfactants taken in 5 ml vials separately and are mixed by vortexing for 10- 15 min. The mixture vials were then kept at 37 ± 1^0C in an isothermal shaker for 72 hours until homogeneity. [37]The homogenate samples were then centrifuged at 10,000 RPM for 20 min at 4 0C. The supernatant was removed by pipetting and the drug concentration was determined by UV Spectrophotometer and drug concentration is calculated with respect to particular oils, co-surfactant, and surfactant. [38]

2. **Construction of Pseudo-ternary Phase Diagram:**

Smedds are formulated using 2 methods
1. Phase Inversion Temperature Method.
2. Construction of Pseudo-ternary Phase Diagram.

➢ Dilution Method.
➢ Water Titration Method.

1. Phase Inversion Temperature Method:

In non- ionic surfactant by changing temperature phase inversion is occured (w/o microemulsion at higher temperature and o/w micro emulsion in low temperature) this method is called phase inversion temperature method. The development of o/w or w/o SMEDDS is dependent on temperature ranges. Instead of temperature alone some other parameters such as pH or salt concentration may be considered. By changing the fraction of water volume with transition time spontaneous radius of curvature can be obtained. [39]

2. Construction of Pseudo-ternary Phase Diagram.

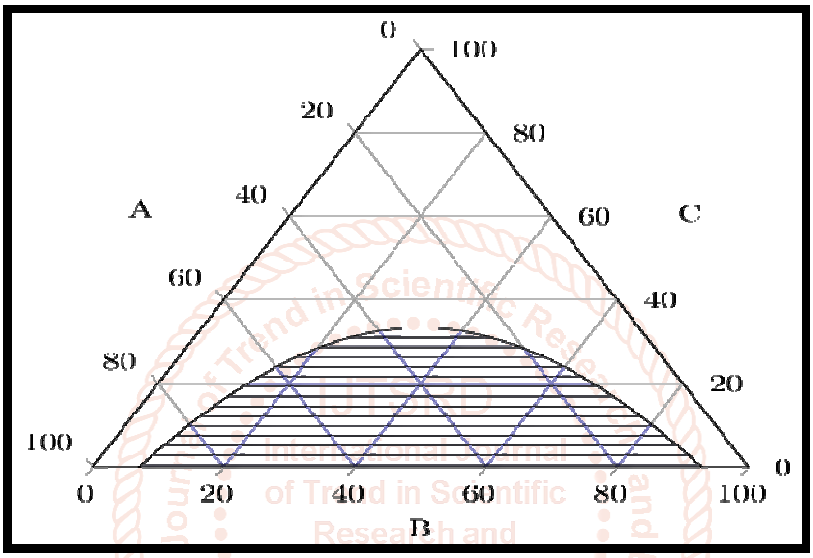
➢ **Dilution method:**

Ternary mixtures with varying compositions of surfactant, co-surfactant and oil were prepared. The percentage of surfactant, co-surfactant and oil decided on the basis of the requirements. Compositions are evaluated for micro emulsion formation by diluting appropriate amount of mixtures with appropriate double distilled water. Globule size of the resulting dispersions was determined by using spectroscopy. The area of micro emulsion

formation in Ternary phase diagram was identified for the respective system in which micro emulsion with desire globule size were obtained. [40]

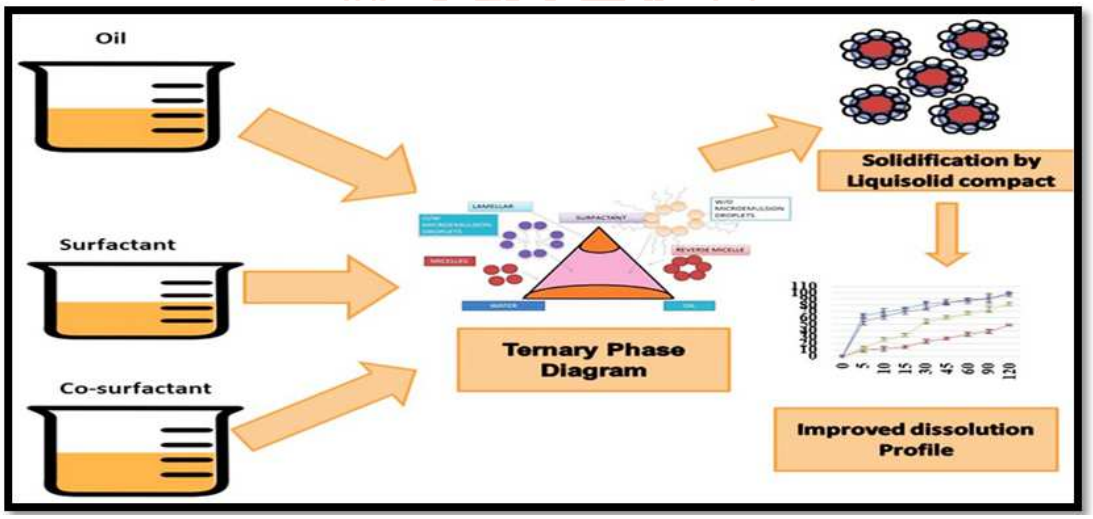
➢ **Water Titration Method:**

The pseudo-ternary phase diagrams were also constructed by titration of homogenous liquid mixtures of oil, surfactant and co-surfactant with water at room temperature. Oil phase, Surfactant and the co-surfactant (surfactant: co-surfactant ratio) were prepared varied from 1:1 to 1:9 and weighed in the same screw-cap glass tubes and were vortexed. Each mixture was then slowly titrated with aliquots of distilled water and stirred at room temperature to attain equilibrium. The mixture was visually examined for transparency. After equilibrium was reached the mixtures were further titrated with aliquots of distilled water until they showed the turbidity. Clear and isotropic samples were deemed to be within the micro emulsion region. No attempts were made to completely identify the other regions of the phase diagrams. Based on the results, appropriate percentage of oil, surfactant and co-surfactant was selected correlated in the phase diagram and were used for preparation of SMEDDS. [41]



PREPARATION OF SMEDDS:

The formulation is developed by mixing oil with a surfactant at 50-60 ℃. The drug is added to the oil phase and then dissolved into the mixture of surfactant and co-surfactant by steady stirring and kept at 50° to 60 ℃ until a clear solution is obtained. [42]



EVALUATION OF SMEDDS:

1. Differential Scanning Calorimetry (DSC):

DSC is utilised to find out the Differential Scanning Calorimetry for SMEDDS. Solid and liquid sample should be applied over the aluminium pan and record the result.[43]

2. Fourier Transform-Infrared Spectroscopy:

By using FT-IR (Fourier transform- infrared) for SMEDDS formulations can be examined. Liquid is placed in sample cell and record the result. If there is any chemical interactions it should be determined by using FT-IR.[44]

3. Visual assessment:

To assess the self-emulsification properties, formulation (60 mg) was introduced into 100 ml of water in a glass flask at 25°C and the contents were gently stirred manually. The tendency to spontaneously form a transparent emulsion was judged as good and it was judged bad when there was poor or no emulsion formation. Phase diagram was constructed identifying the good self-emulsifying region. [45]

4. Macroscopic evaluation:

Macroscopic analysis was carried out in order to observe the homogeneity of microemulsion formulations. Any change in color and transparency or phase separation occurred during normal storage condition (37±2ºC) was observed in optimized microemulsion formulation. [46]

5. Determination of Self emulsification time:

The emulsification time of SMEDDS was determined according to USP 22, dissolution apparatus each formulation added drop wise to 500ml purified water at 37ºC. Gentle agitation was provided by a standard stainless steel dissolution paddle rotating at 50 rpm. Emulsification time was assessed visually. [47]

6. Zeta potential:

The charge of the oil droplets of SMEDDS is another property that should be assessed. The charge of the oil droplets in conventional SMEDDS is negative due to the presence of free fatty acids; this positive n-potential value is preserved following the incorporation of the drug compounds. [48]

7. Droplet Size:

Brownian motion of droplets scatters light; fluctuations in the light scattering are measured by photon correlation spectroscopy, which is converted into particle size in the range of 3 nm to 3 µm. Laser diffractions evaluate the angular distribution of light scattered by the dilute sample and detect droplets from 0.5 nm to 200 µm. Nowadays, freeze-fracture electron microscopy is also used for the surface of the dispersed phase.[49]

8. Rheological determination:

Brookfield viscometer, can be used for evaluation of rheological properties of microemulsion. This study confirms whether the system is o/w or w/o. It should be performed in triplicate.[50]

9. Refractive index

Transparency of the formulation is proved by the refractive index and percent transmittance. The refractive index is measured by Refractometer by placing a drop of solution on slide and then by comparing with water (1.333). If refractive index of system is similar to the refractive index of water (1.333) and formulation have percent transmittance >99%, then formulation has transparent nature. [51]

10. Thermodynamic stability studies:

It is determined by carrying heating cooling cycle, centrifugation test and freeze thaw cycle.

- **Heating cooling cycle:**

Six cycles between refrigerator temperatures 4°C and 45°C with storage at each temperature for not < 48 h was studied. If SMEDDS stable at these temperatures was subjected to centrifugation test.

- **Centrifugation test :**

Passed SMEDDS were centrifuged at 3500 rpm for 30 min using digital centrifuge (Remi motors Ltd). If

SMEDDS did not show any phase separation was taken for freeze-thaw stress test.

➢ **Freeze-thaw cycle:**

Three freeze-thaw cycles between −21°C and +25°C with storage at each temperature for not < 48 h was done for SMEDDS. [52]

11. In-Vitro Release:

The percentage amount of dug release at particular time was determined by USP dissolution apparatus and UV-Spectrophotometer. The test was performed in 900ml basket containing dissolution media (purified distilled water). SMEDDS was placed inside the dialysis bag and place inside the dissolution media under controlled temperature and paddle rotation. At particular interval of time 10ml of sample was withdrawn and replaced with equal amount of fresh dissolution media immediately. Withdrawn sample was filtered and dilute with suitable solvent and analysed spectrophotometrically, and determined the percentage drug release by using Beer lambert's law. [53]

12. Turbidity Evaluation:

Turbidometers are used to measure the turbidity of emulsion. Turbidity demonstrates the growth of emulsion. The turbidity of the resultant emulsions given in nephelometric turbidity units (NTU) is examined most frequently by Hach turbidity meter (Model 2100AN, Loveland, CO.) and the orbecohellle turbidity meter. With the help of turbidity meter, the turbidity can be measured by adding a specific amount of SMEDDS formulation in a suitable medium (0.1 N hydrochloric acid) under continuous agitating (50 rpm) on the magnetic plate at ambient temperature. [54]

APPLICATIONS OF SMEDDS:

➢ **ANTI-HISTAMINE DRUG:**

On developing a drug product with desirable bioavailability is a challenge for sparingly water-soluble drugs such as Fexofenadine hydrochloride. The aim of their project was self microemulsifying drug delivery system (SMEDDS) of Fexofenadine hydrochloride was developed for improving solubility and dissolution rate of drug. The solubility of various prepared formulations was determined by using non - aqueous vehicles. The result of their study was Fexofenadine hydrochloride in SMEDDS formulation was dissolved quickly and completely in dissolution medium (phosphate buffer pH 6.8). [55]

➢ **ANTI DIABETIC DRUG:**

Formulation and In vitro evaluation of Solid -Self-Emulsifying Drug Delivery System (SEDDS) of Glibenclamide. Moto of present study was to produce solid self-micro emulsifying drug delivery system (S-SEDDS) with Aerosil-200 for improvement of dissolution rate of model drug Glibenclamide. From the study it is concluded that, Aerosil-200 can be used to develop S-SEDDS by adsorption technique to increase dissolution rate of poorly water-soluble model drug GBM. The result if this project was S-SMEDDS developed by using Aerosil 200 as a solid carrier to enhance dissolution rate of poorly water-soluble model drug GBM by Adsorption technique. [56]

➢ **SUPER SATURABLE SMEDDS:**

Super saturable-SMEDDS have been developed to overcome the toxic effect of surfactant or GI side effects produced by surfactant when used in very high concentration as typically used in SMEDDS. [57]

➢ **PROTECTION FROM BIODEGRADATION:**

Drugs for which both solubility and degradation is low in the GIT contribute to a low oral bioavailability, SMEDDS is useful for such drugs due to the ability to reduce degradation as well as improve absorption.[57]

CONCLUSION:

The self microemulsifying drug delivery Systems appear to be unique and industrially concrete approach to overcome the setback of low oral bioavailability associated with the lipophillic drugs. The drug selected for this formulation should possess high lipophilicity. There are two techniques for preparation of SMEDDS i.e., adsorption technique and melt granulation technique. Increase oral bioavailability in minimum dose, Site specific targeting of drug towards particular absorption window in GIT and Prevent degradation of drug from the hostile environment in gut. Since a relatively high concentration of surfactants is generally employed in the SMEDDS formulation, toxicity of the surfactant being used should be taken into account.

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REFERENCE:

[1] Kyatanwar AU, Jadhav KR, Kadam VJ. Self microemulsifying drug delivery system (SMEDDS). Journal of Pharmacy Research. 2010 Jan; 3 (2): 75-83.

[2] Tang BC, Jian CG, Xu CH. Development of solid self-microemulsifying drug delivery systems: preparation techniques and dosage forms. Drugs Discovry Today. 2008; 5(6): pg. no. 606-612.

[3] Lipinski CA, Lombardo F, Dominy BW, Feeney PJ. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. Adv Drug Deliv Rev 2012; 64: 4-17.

[4] Pouton CW. Formulation of poorly water-soluble drugs for oral administration: physicochemical and physiological issues and the lipid formulation classification system. Eur J Pharm Sci 2006; 29: 278-87.

[5] Neslihan Gursoy, R. and Benita, S. Self-emulsifying drug delivery systems (SEDDS) for improved oral delivery of lipophilic drugs. Biomedicine & Pharmacotherapy; 2004; 58; 173–182.

[6] Perng CH, Kearney AS, Patel K, Palepu NR, Zuber G. Investigation of formulation approaches to improve the dissolution of SB-210661, a poorly water soluble 5-lipooxygenase inhibitor. Int. J. Pharma, 1998; 176: 31-38.

[7] Khoo SM, Humberstone AJ, Porter CJ, Edwards GA, Charman WN. Formulation design and bioavailability assessment of lipidic self-emulsifying formulations of halofantrine. International journal of pharmaceutics. 1998 Jun 1; 167(1-2): 155-64.

[8] Swarbrick J. Encyclopedia of Pharmaceutical Technology, pdf.

[9] MOHITE PB, HARISHCHANDRE VS. Self-micro emulsifying drug delivery system (SMEDDS): An approach to enhance an oral bioavailability. Caribbean Journal of Sciences and Technology. 2017 Dec 31; 5(1): 01-10.

[10] Hoar TP, Shulman JH. University of Cambridge Nobel Laureates. England, UK. 1943.

[11] Pimple SS, Yeole SE, Chaudhari PD. Self-micro drug delivery system for poorly water soluble drug. Int J Pharm Sci Res 2013; 23(1): 155-62.

[12] Kawakami K, Yoshikawa T, Moroto Y, Kanakao E, Takahuani K, Nishihara Y, Masuda K. Microemulsion formulation for enhanced absorption of poorly soluble Drugs. I. Prescription design, Journal of Control Release, 81, 2002, 75-82

[13] Cortesi R, Espositi E, Maietti A, Menegatti E, Nastruzzi C, Formulation study for the antitumor drug camptothecin: liposomes, micellar solutions and a microemulsion. International Journal of Pharmacy, 159, 1997, 95-103.

[14] Tolle S, Zuberi T, Lawrence MJ, Physiochemical and der-solubilisation properties of N, N-dimethyl-N-(3-dodecyloxy propyl) amine oxide: a biodegradable nonionic surfactant, Journal of Pharmaceutical Science, 89, 2000 798-806.

[15] Khan AW, Kotta S, Ansari SH, et al. (2012). Potentials and challenges in self-nanoemulsifying drug delivery systems. Expert Opin Drug Deliv 9: 1305–17.

[16] Lawrence MJ, Rees GD, Microemulsion-based media as novel drug delivery system, Advanced Drug Delivery Review, 45, 2000, 89-121.

[17] Mahmoud EA, Bendas ER, Mohamed MI. (2009). Preparation and evaluation of self-nanoemulsifying tablets of carvedilol. AAPS PharmSciTech 10: 183–92.

[18] Li L, Yi T, Lam CW. Effects of spray-drying and choice of solid carriers on concentrations of Labrasol® and Transcutol® in solid self-microemulsifying drug delivery systems (SMEDDS). Molecules 2013; 18(1): 545-60

[19] Bowtle, W. J., 2007. Materials, process, and manufacturing considerations for lipid-based hard-capsule formats. Drugs Pharm. Sci. 170, 79-106.

[20] Dokania, S., Joshi, A. K., 2015. Self-microemulsifying drug delivery system (SMEDDS)—challenges and road ahead. Drug Deliv. 22 (6), 675-690

[21] Zhu JX, Tang D, Feng L, Zheng ZG, Wang RS, Wu AG, et al. Development of self-microemulsifying drug delivery system for oral bioavailability enhancement of berberine hydrochloride. Drug Dev Ind Pharm 2013; 39 (3): 499-506.

[22] Reiss H: Entropy-induced dispersion of bulk liquids. Journal of Colloid and Interface Science 1975; 53(1): 61- 70.

[23] Agrawal S, Giri TP, Tripathi Dl, Ajazuddin and Alexander A: A review on novel therapeutic strategies for the enhancement of solubility for hydrophobic drugs through lipid and surfactant based self microemulsifying drug delivery system: a novel approach. American Journal of Drug Discovery and Development 2012; 2(4): 143-83

[24] Porter CJ, Charman WN: In-vitro assessment of oral lipid based formulations. Advanced Drug Delivery Reviews 2001; 50 (1): S127-47.

[25] Shah NH, Carvajal MT, Patel CI, Infeld MH and Malick AW. Self-emulsifying drug delivery systems (SEDDS) with polyglycolized glycerides for improving in vitro dissolution and oral absorption of lipophilic drugs. Int J of Pharm 1994; 106: 15–23.

[26] Stegemanna S, Leveillerb F. When poor solubility becomes an issue: from early stage to proof of concept. Eur J Pharm Sci 2007; 31: 249-61.

[27] Mittal P, Seth N and Rana AC: Self-microemulsifying drug delivery system (SMEDDS): An alternative approach for hydrophobic drugs. International Journal of Natural Product Science 2012; 1: 80.

[28] Shah, A., Thool, P., Sorathiya, K., Prajapati, H., Dalrymple, D., Serajuddin, A. T. M., 2018. Effect of different polysorbates on development of self-microemulsifying drug delivery systems using medium chain lipids. Drug Dev. Ind. Pharm. 44 (2), 215-223

[29] Misal RS, Potphode VR and Mahajan VR: Review On: New approaches in self microemulsifying drug delivery system. Res J of Pharm and Techno 2017; 10(4): 1215.

[30] McConville C, Friend D. Development and characterisation of a self-microemulsifying drug delivery systems (SMEDDSs) for the vaginal administration of the antiretroviral UC-781. Eur J Pharm Biopharm 2013; 83 (3): 322-9.

[31] Gao P: Design and development of self-emulsifying lipid formulations for improving oral bioavailability of poorly water-soluble and lipophilic drugs. In formulating poorly water soluble drugs. Springer, New York, NY 2012: 243- 266.

[32] Shinde et al. (2013). Novel Approaches for Development and Characterization of SMEDDS: Review. International Journal of Current Pharmaceutical Research, 5(4), 5-12

[33] Ingle L. M. (2013). New Approaches for Development and Characterization of SMEDDS. International Journal of Pharmacy and Pharmaceutical Science Research, 3(1), 7-14

[34] Azaz E, Donbrow M, Hamburger R. (1973). Incompatibility of non-ionic surfactants with oxidisable drugs. Pharm J 211: 15.

[35] Kumar, P. and Mital, K. L. Handbook of microemulsion: Science and Technology. Marcel Dekker, New York, Basel; 1999.

[36] Manyam N. (2011). Recent advances in self-emulsifying drug delivery system. International Journal of Review in Life Sciences, 1(4), 206-214.

[37] Shailesh T. Prajapati Harsh A, Joshi Chhaganbhai N. Patel. (2013)., Preparation and Characterization of Self-Micro emulsifying Drug Delivery System of Olmesartan medoxomil for Bioavailability Improvement., Journal of Pharmaceutics. 2013; 2: 01-09.

[38] Ranpise AA and Wagh MP: Lipid-based self-microemulsifying drug delivery system: A novel approach for lipophilic drugs. Journal of Pharmacy Research 2018; 12(4): 560

[39] Patel PK, Patel MR, Patel KR. A review on self -micro emulsifying drug delivery systems. Adv Res in Pharma and Bio, 2014; 4(1): 590-598.

[40] Latika M. Ingle New Approaches for Development and Characterization of SMEDDS International Journal of Pharmacy and Pharmaceutical Science Research 2013; 3(1): 7-14.

[41] Koushik yetukuri and preethi sudheer Approaches To Development Of Solid - Self Micron Emulsifying Drug Delivery System: Formulation Techniques And Dosage Forms: A Review. IJPSR, 2012; vol. 3(10): 3550-3558

[42] Turner SR, Siano DB and Bock J: A Microemulsion Process for Producing Acrylamide-Alkyl Acrylamide Copolymers. U. S. Patent 1985: 4; 521-580.

[43] Nirali Padia, Arunkumar Shukla and Pragna Shelat. Development and characterization of fenofibrate selfmicroemulsifying drug delivery system (smedds) for bioavailability enhancement. Bulletin of Pharmaceutical Research 2015; 5(2): 59-69. 39.

[44] Singh D, Ranga S. A review on self-emulsifying drug delivery system: promising approach to enhance bioavailability. J of Drug Dis. Thera., 2014; 2(17): 01-12

[45] Kamble V A, Jagadale D M, Kdam V J. self microemulsifying drug delivery system Int. J Pharma Bio sci. 2010 v1(2) 1-9

[46] Shukla Jill B., Koli Akshay R., Ranch Ketan Self Micro Emulsifying Drug Delivery System An International Journal Of Pharmaceutical Sciences Vol-1, Issue-2, 2010, 14-33

[47] Mahajan HD, Shaikh T., Bhaviskar D. Design and development of self-emulsifying drug delivery system. IJPS 2011: 3 163-166

[48] Craig DQ, Barker SA, Banning D, Booth SW, An investigation into the mechanisms of self-emulsification using particle size analysis and low frequency dielectric spectroscopy, International Journal of Pharmacy, 114, 1995, 103-110

[49] Vyas SP and Khar RK: Submicron emulsion. in: targeted and controlled drug delivery novel carriers systems. India: CBS Publishers and Distributors 2002: 291–94.

[50] Harshal DM, Rajendra DW, Tanvvir S. Design and development of self-micro emulsifying drug delivery system. Int J Curr Pharm Res 2011; 5(4): 163-5. 22.

[51] Sha X, Wu J, Chen Y, Fang X. Self-microemulsifying drug-delivery system for improved oral bioavailability of probucol: Preparation and evaluation. Int J Nanomedicine 2012; 7: 705-12.

[52] More HN, Hazare AA. Practical Pharmaceutics (Physical pharmacy). 1st ed. Kolhapur: Manas Prakashan; 2004. p. 86-105.

[53] Attama AA, Nzekwe IT, Nnamani PO, Adikwu MU and Onugu CO: The Use of Solid Self-Emulsifying Systems in the Delivery of Diclofenac. International Journal of Pharmaceutics 2003; 262(1-2): 23-8.

[54] Nazzal S, Smalyukh II, Lavrentovich OD and Khan MA: Preparation and in-vitro characterization of a eutectic based semisolid self-nanoemulsified drug delivery system (SNEDDS) of ubiquinone: mechanism and progress of emulsion formation. International Journal of Pharmaceutics 2002; 235(1-2): 247-65.

[55] Akash M Patel, Jitul B Patel, Tejas B Patel, B. N. Suhagia, Tushar R Patel, preparation and evaluation of self microemulsifying drug delivery system for fexofenadine hydrochloride, Journal of Drug Delivery & Therapeutics; 2013, 3(4), 26-32.

[56] Maria Saifee, Sharda Zarekar, Vinay. U Rao, Zahid Zaheer, Reshma Soni, Shailesh Burande. Formulation and In vitro evaluation of SolidSelf- Emulsifying Drug Delivery System (SEDDS) of Glibenclamide. American Journal of Advanced Drug Delivery, ISSN 2321-547